

Penicillinase-producing gonococcal strains in Zambia*

Observations on treatment failures

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SUMMARY Penicillinase-producing strains of *Neisseria gonorrhoeae* (PPNG) were detected in nine out of 27 (3·2%) treatment failures in 310 cases of acute gonococcal urethritis in men in Lusaka, Zambia. Minimum inhibitory concentrations of penicillin for 17·2% of 233 gonococcal isolates were $\leq 0\cdot05$ $\mu\text{g/ml}$, for 38·2% between 0·125 and 0·25 $\mu\text{g/ml}$, and for 46·6% $\geq 0\cdot5$ $\mu\text{g/ml}$.

At present the prevalence of PPNG in African countries is not known but is likely to increase rapidly unless simplified control schemes are adopted within the existing primary health care programmes. Endemic pockets of PPNG in a few countries can threaten worldwide efforts to control gonorrhoea.

Introduction

Although penicillin is still the drug of choice for the treatment of gonorrhoea, continued surveillance of the susceptibility of gonococci to penicillin has become mandatory because of increasing drug resistance. The emergence of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) in 1976, and their increasing prevalence in many parts of the world,¹ has been a further serious challenge to effective antibiotic treatment. It has been observed that PPNG not only survive high doses of various penicillins but are also less susceptible to many other antibiotics.^{2,3} Reports from many countries⁴⁻⁷ indicate a higher prevalence of gonorrhoea in Africa than elsewhere and that gonococcal strains which are less susceptible to penicillin are also more prevalent.⁸⁻¹² Zambia is no exception, high incidences of gonorrhoea have been reported among patients attending the sexually transmitted diseases clinic in Lusaka,¹³ in pregnant women,¹⁴ and in patients with pelvic inflammatory disease.¹⁵

In this paper we have reviewed the minimum inhibitory concentrations (MICs) of penicillin to 233

gonococcal strains and the clinical and laboratory aspects of 27 cases of treatment failure.

Patients and methods

DIAGNOSIS

Between August 1980 and February 1981 gonococcal infection was diagnosed in 574 men. The presence of typical Gram-negative intracellular diplococci in urethral smears was considered adequate for diagnosis. Specimens for culture were also taken from 420 men, and gonococci were isolated in 391.

TREATMENT

Of these 574 men, 265 received aqueous procaine penicillin (APPG) 4·8 megaunits by injection with probenecid 1g orally, 185 amoxycillin 3 g in a single oral dose, and 124 an injection of spectinomycin 2 g.

FOLLOW UP

After treatment 485 men had test-of-cure cultures performed after 48 hours, and 351 attended for a second examination after two weeks. Treatment failure was diagnosed if gonococci reappeared either in Gram-stained urethral smears or in cultures during the two-week follow-up period in the absence of further sexual contact. By these criteria treatment failure was suspected in 27 cases, of which 23 were confirmed by positive culture results. In all the 27 cases the initial drug regimen was repeated, and

*A slightly modified version of this paper was presented at the Second IUVD Conference, Dakar, 4-9 May 1981

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Accepted for publication 24 July 1981

patients were reassessed. If the second treatment also failed to effect cure, patients were retreated with spectinomycin 2 g.

BACTERIOLOGY

Thayer-Martin medium, containing vancomycin, colistin, and nystatin, was used for primary isolation of gonococci. Urethral discharge or a scraping obtained with a sterile 3-mm platinum loop was directly plated in the clinic and incubated in a candle-extinction jar at 37°C for 24 to 48 hours. Positive cultures were identified by typical colonial appearance, oxidase reaction, and examination by Gram's stain.

MINIMUM INHIBITORY CONCENTRATIONS

An agar plate dilution technique was used to determine the MICs of penicillin. Saline suspension of the test strains and a control strain (*Staphylococcus aureus* ATCC 25923), corresponding to a McFarland No 5 tube, were prepared and a 3-mm loopful of these suspensions used to inoculate chocolate agar plates enriched with Isovitalex, containing doubling dilutions of benzyl penicillin from 2.0 to 0.0125 µg/ml, and a control plate without penicillin. (This standardisation of the inoculum was not performed during the earlier part of the study.) The inoculated plates were inspected for growth after 24 hours' incubation, and the MIC was taken as the lowest concentration at which no visible growth occurred.

PENICILLINASE PRODUCTION

A total of 310 gonococcal isolates were also screened for penicillinase production by a rapid iodometric method.¹ Penicillinase-positive and penicillinase-negative reference strains (CDC-76-073389, F-18) were tested with each batch. Ten PPNG strains were identified (one from a patient successfully treated with spectinomycin) and their antibiotic sensitivities also tested with discs of penicillin 6 µg, ampicillin 25 µg, amoxycillin 25 µg, co-trimoxazole 25 µg and tetracycline 30 µg. Isolates with an inhibitory zone of more than 10mm in diameter were considered sensitive.

Results

SENSITIVITIES

MICs of penicillin for 233 gonococcal strains, including those from 23 of 27 treatment failures, are shown in the table. MICs of only 17.2% of strains were within the sensitive range (≤ 0.05 µg/ml). Intermediate sensitivity (0.125-0.25 µg/ml) was observed for 38.2% of strains, and 46.6% showed a

TABLE Penicillin sensitivities of 233 gonococcal isolates

MICs of penicillin (µg/ml)	No (%) of strains	No of treatment failures
0.0125-0.05	40 (17.2)	0
0.125-0.25	89 (38.2)	5
0.5-2.0	104 (44.6)	18*

* Includes 9 PPNG Strains

greater degree of resistance (≥ 0.5 µg/ml). MICs of five strains from treatment failures were in the intermediate sensitivity range, and 18 strains, including nine PPNG, had MICs of >0.5 µg/ml. By the disc test all the 10 PPNG strains were resistant to 6 µg of penicillin and to 25 µg each of ampicillin and amoxycillin.

Three strains were sensitive to tetracycline and only one was sensitive to co-trimoxazole.

TREATMENT

In all the nine treatment failures due to PPNG there was little or no response to the initial drug regimen (whether with APPG or amoxycillin), and repeat treatment was also ineffective. Eighteen failures were associated with non-PPNG strains, and in six of these there was little or no response to initial treatment. In the remaining 12 cases there was an initial response (first culture results were negative), but the infection recurred within 10 days. In the 16 cases seen after the repeat treatment, failure occurred again in eight.

Retreatment with spectinomycin was successful in eight of the nine infections with PPNG that were followed and in all eight non-PPNG infections.

Discussion

It is now confirmed that a great majority of gonococcal strains in Lusaka are relatively resistant to penicillin. We believe this results from the widespread use of inadequate penicillin dosage regimens for gonorrhoea. Until recently the prevailing practice in Zambia was to treat patients with any genital ulcer or discharge with a dose of 0.6 megaunits of penicillin daily for 10 days. Antibiotics are available free of charge and hence are widely used by medical staff for a variety of minor problems. Furthermore self-treatment with a few capsules of ampicillin is commonly practised by patients with gonorrhoea. Thus, selection of increasingly resistant gonococci is a predictable result. Despite the low susceptibility of gonococci to penicillin in vitro, however, satisfactory cure rates are still obtained with high doses of penicillin. On the other hand, the problem of PPNG appears to be more serious, since they were responsible for 33% of

the treatment failures. Although their prevalence is low (3.2%) in Lusaka, all the infections were acquired within Zambia, and it is possible that some areas in the country have a higher prevalence of PPNG.

Apart from Zambia, PPNG have so far been identified in West Africa¹⁶ and Zaire (Piot, personal communication). The size of the problem in other African countries is not yet known, but it can be presumed that the serious situation reported in a few countries is only the tip of an iceberg. Special STD clinics are established at a few teaching centres and, in general, diagnosis remains largely presumptive on clinical presentation alone and treatment practices are suboptimal. Furthermore, follow-up is poor and neither treatment failures nor sexual contacts are identified. Thus, there can be little doubt that the prevalence of PPNG will rise within a few years throughout Africa.

Treatment of PPNG infections will be a serious problem since the choice of alternative therapy is limited to a few drugs, which at the moment are prohibitively expensive for the inadequate health budgets. In addition to these problems there is little hope for an immediate remedy because many countries do not have enough trained staff and resources to carry out large-scale control programmes. The only practical approach would be to adopt a simplified control strategy within the primary health care programmes, which many countries are presently planning. STD management at all the health centres, large and small, must be improved as a priority before any community-based control is attempted. Lack of awareness and concern among clinicians is part of the problem, and medical personnel must be made aware of the special problems of gonorrhoea and be motivated to take appropriate action. Staining by Gram's method is a simple procedure that should be used routinely for initial diagnosis and for tests of cure. All treatment failures should be identified and retreated with spectinomycin.

Providers of health care in African countries must pay serious attention to the increasing problems of

gonorrhoea control. Zambia has taken the first step forward in developing a small network of special clinics in the provinces, and a national STD control programme has recently been launched. As far as PPNG are concerned, it is obvious that endemic pockets in a few countries can threaten the efforts being made all over the world; hence nothing short of a concentrated global action can be expected to provide an adequate remedy.

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